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When differences matter: rTMS/fMRI reveals how differences in dispositional empathy translate to distinct neural underpinnings of self-other distinction in empathy

Ruff, Christian C ; Bukowski, Henryk ; Tik, Martin ; Silani, Giorgia ; Windischberger, Christian ; Lamm, Claus

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**When differences matter: rTMS/fMRI reveals how differences in dispositional empathy
translate to distinct neural underpinnings of self-other distinction in empathy**

RUNNING HEAD: SELF-OTHER DISTINCTION RTMS/FMRI

Bukowski^{1*}, H., Tik², M., Silani³, G., Ruff⁴, C.C., Windischberger², C., & Lamm¹, C*.

¹Social, Cognitive and Affective Neuroscience Unit, Department of Basic Psychological Research and Research Methods, University of Vienna, Liebiggasse 5, 1010 Vienna, Austria; hbbukowski@gmail.com, claus.lamm@univie.ac.at

²MR Center of Excellence, Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Lazarettgasse 14, 1090 Vienna, Austria ; martin.tik@meduniwien.ac.at, cwind@univie.ac.at

³Department of Applied Psychology: Health, Development, Enhancement and Intervention, University of Vienna, Liebiggasse 5, 1010 Vienna, Austria; giorgia.silani@univie.ac.at

⁴Zurich Center for Neuroeconomics (ZNE), Department of Economics, University of Zurich, Blüemlisalpstrasse 10, 8006 Zurich, Switzerland; christian.ruff@econ.uzh.ch

*Corresponding authors.

Keywords: empathy; fMRI; cTBS; self-other distinction; egocentric bias

Abbreviations: cTBS: continuous theta burst stimulation; rTMS: repeated transcranial magnetic stimulation; rSMG: right supramarginal gyrus; QCAE: Questionnaire of Cognitive and Affective Empathy; AMT: Active motor threshold

Highlights:

- Combined rTMS-fMRI looked at the rSMG, an area previously involved in emotional egocentricity
- cTBS on the rSMG tended to enhance rather than to disrupt self-other distinction performance
- Dispositional empathic understanding predicts rTMS effects on behaviour and neural correlates
- Distinct neural networks linked with opposite effects of rTMS on self-other distinction

Abstract

Self-other distinction is crucial for empathy, since it prevents the confusion of self-experienced emotions with those of others. We aimed to extend our understanding of the neurocognitive mechanisms of self-other distinction. Thirty-one female participants underwent continuous theta burst transcranial magnetic stimulation (cTBS) targeting the supramarginal gyrus (rSMG), a sub-region of the temporoparietal junction previously shown to be involved in self-other distinction, and the vertex, a cortical control site. Right after stimulation they completed a visuo-tactile empathy task in an MRI scanner. Self-other distinction performance was assessed by differences in emotion judgments and brain activity between conditions differing in the requirement for self-other distinction. Effects of rSMG-cTBS (compared to vertex cTBS) on self-other distinction depended on dispositional empathic understanding: they decreased self-other distinction in participants with lower dispositional empathic understanding, but increased it in participants with higher empathic understanding. On the neural level, this inverse relationship between disposition and self-other distinction performance translated into a reduction or an increase of cTBS-induced rSMG activity, in persons with lower and higher dispositional empathy, respectively. Moreover, the differences in rSMG activity were associated with two anatomically and functionally distinct networks. These findings open up novel perspectives on the causal role of rSMG in self-other distinction and empathy. They also suggest that considering individual differences may yield novel insights into how brain stimulation affects higher-level affect and cognition, and its neural correlates.

1. Introduction:

Our emotional states can interfere with our empathic appreciation of how another person feels; conversely, others' emotions can sometimes intrude and confuse the way we feel ourselves. These barriers to empathic understanding are referred to as the *egocentric* and *altercentric* biases, respectively, and can be overcome via *self-other distinction*, a mechanism enabling the regulation and resolution of discrepancies as well as confusions between self-experienced feelings and those experienced by another person (Lamm, Bukowski, & Silani, 2016). Social neuroscience has recently set out to investigate the neural underpinnings of self-other distinction in empathy (Lamm et al., 2016; von Mohr, Finotti, Ambroziak, & Tsakiris, 2019), by means of tailored experimental paradigms. In one study (Silani, Lamm, Ruff, & Singer, 2013) combining behavioral, neuroimaging and brain stimulation experiments, we had shown that the right supramarginal gyrus (rSMG) plays a specific and causal role in empathy-related self-other distinction. The present study builds up on this prior evidence. Here, we investigated the neural network underpinning empathy-related self-other distinction, by combining theta burst transcranial magnetic stimulation (cTBS) of the rSMG with measuring brain activity using functional magnetic resonance imaging (fMRI). The main aim of this combined brain stimulation-neuroimaging approach was to gain direct access to the neural networks by which rSMG implements self-other distinction in empathy.

Handling discrepancies in self-vs. other-related representations is a prevalent mental process since we see, feel, or believe while inferring what others see, feel, or believe. For non-affective mental states, the variability and fallibility of our capacity to distinguish self-experienced mental states (e.g., beliefs, goals, and visual perspectives) from those experienced by others is well-documented, and is typically demonstrated by behavioral indicators of egocentric biases and, more recently, also altercentric biases (Bukowski & Samson, 2017; Krueger & Clement, 1994; Royzman, Cassidy, & Baron, 2003). Research on biased inferences in the affective domain, i.e., in empathy, had been absent until fairly recently, when novel experimental tasks have been introduced (Silani et al., 2013; Steinbeis, Bernhardt, & Singer, 2015; von Mohr et al., 2019). What is common to these tasks is that they experimentally manipulate the emotional states of their participants and those of another person that the participant is empathizing with, in ways that self-other emotions are either congruent or incongruent. In the task version of Silani et al. (2013), which we used here as well, this is achieved by means of visuo-tactile stimulations tailored to induce transient pleasant and unpleasant emotions. For instance, viewing a picture labeled 'you' depicting a slug and being

touched on their hand by a material resembling a slug was used to induce an unpleasant emotional response, while viewing a picture labeled ‘your colleague’ depicting a baby brush informed the participant that her colleague was being touched on her hand by a baby brush, which would induce a pleasant emotional response for her colleague. Using such a setup revealed empathic judgements to be egocentrically biased, in the sense that if the participant experienced an emotion of opposite valence than the one of her colleague (e.g., the participant felt disgusted while her colleague was pleased), she would perceive her colleague’s emotion as less intense (e.g., less pleasant) than if the participant had experienced an emotion of the same valence (e.g., both being disgusted). This reduction in rated intensity of the other person’s emotion reflects the extent our empathic judgements are biased (“drawn towards”) one’s own emotion (see Figure 1). The presence of this egocentric bias in empathy has been corroborated by additional studies, including ones that had induced emotions in other ways than via visuo-tactile stimulation (Hoffmann, Singer, & Steinbeis, 2015; Steinbeis et al., 2015; Steinbeis & Singer, 2014; Tomova et al., 2014; von Mohr et al., 2019).

In terms of the neural correlates, the study of Silani et al. (2013) also identified across two fMRI experiments the right supramarginal gyrus (rSMG) to be more active when empathically judging emotions that are incongruent with the participant’s self-experienced emotion. In other words, rSMG was engaged to a stronger extent in trials prone to be influenced by egocentric bias. The rSMG is an associative area located in the anterior section of larger multimodal area named the temporo-parietal junction whose most posterior section is consistently found to be more active in Theory of Mind studies with trials prone to non-affective egocentric biases, that is, when inferring the other person’s mental state that is conflicting with the participant’s self-experienced mental state, such as opposite beliefs, goals, or visual perspectives (Bukowski & Lamm, 2017; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014; Schurz, Tholen, Perner, Mars, & Sallet, 2017). In a follow-up rTMS experiment, Silani et al. (2013) also found a higher egocentric bias in a group whose whose rSMG was neuromodulated via “inhibitory” 1 Hz rTMS than a group who had rTMS on the vertex (a cortical control site). This was suggestive of a causal role of rSMG in regulating egocentric biases, and that rSMG activity should be considered as reflecting the extent of regulation or overcoming of egocentric bias, rather than being linked to the occurrence of egocentric bias. In a similar vein, in the study by Steinbeis et al. (2015), functional connectivity with the rSMG increased as a function of lower egocentric bias in the superior parietal cortex and the lateral prefrontal cortex, suggesting that rSMG implements self-other distinction by means of engaging a

cognitive control network. Relatedly, Tomova et al. (Tomova et al., 2016) found that the group who was more successful at modulating their automatic aversive response – and thus implementing self-other distinction - when seeing a syringe injected into an anesthetized hand activated significantly more the lateral prefrontal cortex (see also Tomova et al., 2019; <https://psyarxiv.com/fkxs9>). The involvement of cognitive control to implement self-other distinction and prevent egocentric biases was further demonstrated by Hoffman et al. (2015), who found the egocentric bias negatively correlated with conflict-handling performance. Notably, these findings are well in line with evidence linking cognitive control to self-other distinction performance for non-affective mental states (e.g., Carlson & Moses, 2001; Qureshi, Apperly, & Samson, 2010).

While the aforementioned findings support the hypothesis that the rSMG somehow implements self-other distinction via cognitive control, a study combining behavioral, fMRI, and TMS measures in a combined approach has so far been missing. It is therefore unclear which neural networks are associated with rTMS-induced and rSMG-related changes in self-other distinction in the domain of empathy. Critically, the hypothesis that increased engagement of rSMG implements self-other distinction also appears somewhat at odds with fMRI studies that have consistently documented rSMG activation in empathy tasks where egocentric interference seems implausible or at least much reduced - such as, e.g., in empathy for pain paradigms where the participant merely observed someone in pain, while being in a neutral state him- or herself (for meta-analyses, see Fallon, Roberts, & Stancak, 2018; Jauniaux, Khatibi, Rainville, & Jackson, 2019; Lamm, Decety, & Singer, 2011). In addition, the rSMG is consistently found co-active and functionally connected to the bilateral insula and the anterior middle cingulate cortex (e.g., (Mars et al., 2012; Steinbeis et al., 2015); see also neurosynth.org/locations/68_-38_36_6/), a network typically found in paradigms tapping into affect sharing. Affect sharing is a basic ability rooted in emotional contagion and demonstrated in many mammals (for reviews, see Adriaense, Koski, Huber, & Lamm, 2020; de Waal & Preston, 2017), and recently also in birds (e.g., Adriaense, Martin, Schiestl, Lamm, & Bugnyar, 2019). In humans, this ability seems anatomically and functionally distinct from empathic understanding, and might not require or entail self-other distinction (Kanske, Böckler, Trautwein, Lesemann, & Singer, 2016; Lamm et al., 2016; Lamm, Rütgen, & Wagner, 2019). Importantly, at the behavioral level, affect sharing is mainly measured by how much one is sensitive to another person's emotional state. Yet, sensitivity does not imply

understanding and sensitivity is usually measured in conditions ensuring an initial neutral emotional state, as if we were empty mental containers ‘waiting to be filled’ by another’s emotional or mental state. To sum up the current understanding, since rSMG is recruited both in self-other distinction and affect sharing paradigms, the role of this area in empathy as well as the neural networks by which it may implement self-other distinction are unclear. This directly motivated the present study.

Self-other distinction has so far been predominantly investigated by focusing on egocentricity, both in empathy and Theory of Mind research. A burgeoning body of literature has been pointing out, though, that altercentric biases – i.e., spontaneously computing another person’s mental state when judging our own mental state - also offers compelling insights into the neural underpinning and the behavioral accuracy of self-other distinction (Brass, Ruby, & Spengler, 2009; Hoffmann et al., 2016; Santiesteban et al., 2012). Moreover, two behavioral ‘mega-analyses’ (Bukowski & Samson, 2017; Bukowski, Silani, Riva, Tomova, & Lamm, 2016) have recently documented significant individual differences in both altercentric and egocentric biases in paradigms manipulating both the level of conflict between self-other mental states (congruent or incongruent) and the perspective to judge (self or other), such as in the visuo-tactile empathy task employed by Silani et al. (2013). Moreover, these mega-analyses revealed that the extent individuals show altercentric and egocentric biases forms a single dimension – self-other distinction – that captures the extent of overall bias, and along which substantial individual differences exist.

Until recently, individual differences in empathy and related phenomena were almost exclusively studied via questionnaires, among which empathic understanding is often captured by the Perspective Taking sub-scale of the Interpersonal Reactivity Index (Davis, 1983), the Cognitive Empathy sub-scale of the Empathy Quotient (Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004), and the Cognitive Empathy sub-scale of the Questionnaire of Cognitive and Affective Empathy (QCAE; (Reniers, Corcoran, Drake, Shryane, & Völlm, 2011), which integrates items of the two former questionnaires. Performance and neural activity during social cognition tasks are also now used to measure individual differences in empathy, which have been linked with (1) questionnaires such as the QCAE in Lockwood et al. (Lockwood, Ang, Husain, & Crockett, 2017; Lockwood, Apps, Valton, Viding, & Roiser, 2016), (2) empathic performance (e.g., Kanske et al., 2016), and (3) rTMS effects on empathy (Paracampo, Pirruccio, Costa, Borgomaneri, & Avenanti,

2018). In short, individual differences in empathy are increasingly documented to explain variability in performance, neural activity, and rTMS effects (see Discussion for an extended argument).

The main aim of our study was to investigate the neural networks by means of which cTBS of the rSMG affected self-other distinction in empathy. In line with recent affective self-other distinction studies (Bukowski, Silani, Riva, Tomova, & Lamm, n.d.; Hoffmann et al., 2016), we aimed to focus not only on egocentric, but also on altercentric biases. In addition, in order to overcome some of the limitations of our own previous work (Silani et al., 2013), we (1) adopted a within-subject design to exclude the possibility that the rTMS finding gained with a between-subject design stemmed from small-sample inter-group differences, (2) combined offline cTBS with fMRI to measure whole-brain effects of cTBS, (3) doubled the number trials to increase reliability, and (4) analyzed and interpreted both egocentric and altercentric biases as indices of self-other distinction performance. We hypothesized *a priori* the presence of significant egocentric and altercentric biases, attesting the fallibility of the participants' self-other distinction capacity, and a predominantly inhibitory effect of cTBS on self-other distinction, leading to increased biases. We also included a measure of dispositional empathic understanding to control for individual differences (i.e., the variability) in self-other distinction, but no *a priori* hypothesis was specified regarding its potential moderating role.

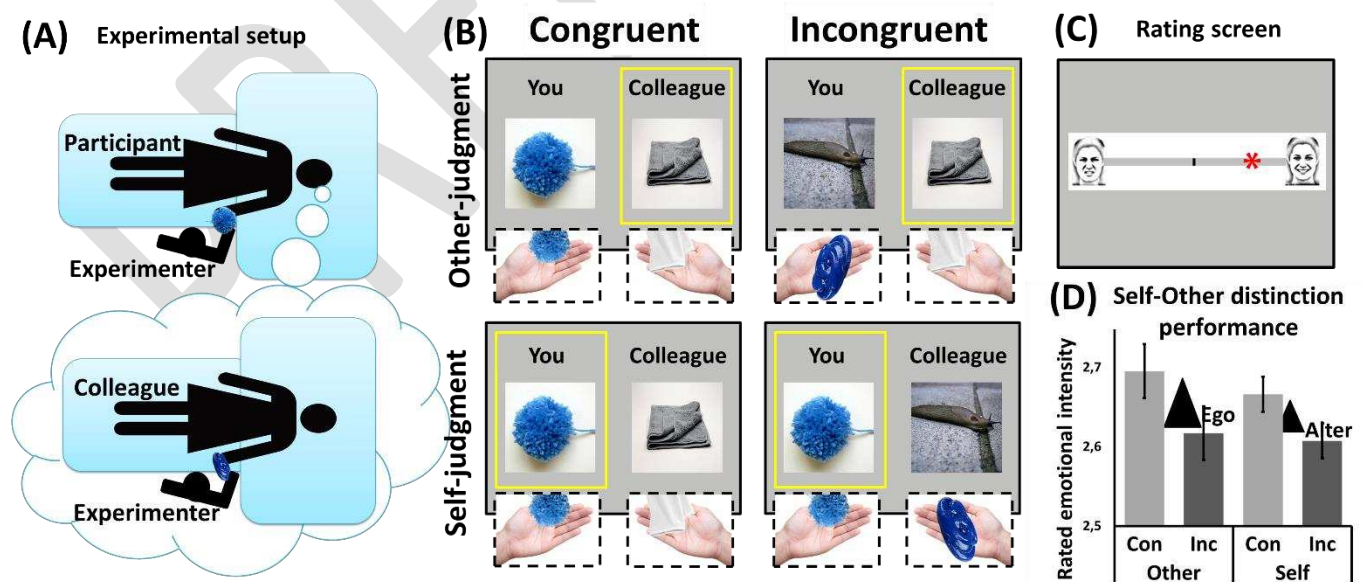


Figure 1. Behavioral measures and experimental conditions: (A) Participants were lying in the MRI scanner and were touched by a pleasant or unpleasant object, in synchrony with a display on screen of two objects: an object matching (in terms of the quality of touch) the object they were

touched with themselves, and another object indicating the quality of touch another participant was supposedly experiencing. (B) Depending on the valence of the self-experienced emotion and the depicted emotional experience of the second participant, self- and other-related emotions could be congruent (both pleasant, or both unpleasant) or incongruent (pleasant/unpleasant, or vice versa). (C) Emotion ratings were entered on a nine-step rating scale ranging from -4 (very unpleasant) to +4 (very pleasant) to judge the self-experienced or the second participant's emotion in the self- and other-perspective blocks of trials, respectively. (D) Scores when rating unpleasant stimuli were reversed to form, with pleasant stimuli ratings, a single score of rated emotional intensity. Ratings in the vertex (control) cTBS session (mean \pm 95% confidence intervals) show that participants were biased: their judged emotional experiences were rated as less intense in incongruent than congruent trials. This reduction of intensity reflects an egocentric bias (i.e., own emotion influencing appreciation of other person's emotion) as well as an altercentric bias (i.e., other person's emotion influencing appreciation of own emotion) when judging the colleague's and the self-experienced emotion, respectively. Strong biases – i.e., decreased emotional intensity in incongruent conditions – indicate poor self-other distinction performance.

2. Material and methods

2.1. Transparency and ethics:

In accordance with transparency and openness guidelines, the study data, analysis codes, and materials have been archived on a publicly available repository (<https://osf.io/hfnk5/>). No part of this study has been pre-registered prior to the research being conducted. We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, and whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in this study.

This study and all its procedures were performed in compliance with the Declaration of Helsinki (2013) and has been approved by the ethics committee of the Medical University of Vienna (reference ECS 1025/2015).

2.2. Sample:

A power analysis conducted with G*Power 3.1 ($\alpha = 0.05$, $1-\beta = 0.95$) on the between-subject effect of rTMS on rSMG in Silani et al. (2013, rTMS experiment) indicated a requirement of 28 participants for a within-subjects rTMS design. Thus, we included thirty-one female participants ($M_{\text{age}} = 21.90$; $SD_{\text{age}} = 3.39$) in the study. Only female participants were recruited for consistency with previous work (Silani et al., 2013) and because sex differences on this task had been documented as well (Tomova et al., 2014). All participants were right-handed (as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), had normal or corrected-to-normal vision, and reported no past or present neurological or psychiatric disorder. Prior to and on the day of

testing, but prior to beginning the experiment, all participants were checked for the established exclusion criteria for MRI (Kanal, Shellock, & Committee, 1992) and TMS (Rossi, Hallett, Rossini, & Pascual-Leone, 2011) (e.g., metallic hardware in body, sleep deprivation, drug abuse, or previous neurosurgery). All participants provided a written consent for participation, received € 80.00 for participation, and undergraduate students additionally received credits.

2.3. Procedure:

Each participant completed two sessions one week apart during which cTBS was applied on either the rSMG or vertex (with order counterbalanced across the sample). Behavioural and fMRI data were acquired before cTBS for training and localizer purposes, and then again right after cTBS, during performance of the visuotactile empathy task (see Figure 2). Prior to arrival at the neuroimaging facility, participants received information that the experiment would include cTBS and MRI and the associated risks and inclusion criteria, and that it would be completed along with another participant. They completed a screening survey assessing medical history and dispositions for empathy and related constructs (cf. Screening section).

On the day of testing, the participant sat in the waiting room next to another student (who in reality was a confederate of the experimenter) that she had never met or interacted with before. This other student was part of the research team but acted as the second participant to set the interactive context of the empathy task (i.e., to be the person whose feelings would be judged by the real participant during the empathy task). The confederate student was the same person on the following testing session and trained to show similar type and content of interactions during the waiting period with all participants. The participant and the confederate then received the general instructions, filled in the medical screening, were familiarized with the MRI and TMS equipment, followed by a short training with the empathy task, and eventually filled in the consent form. During the first day of testing, each participant went into the scanner first for 40 min during which six 8-minute runs of MRI images were collected (scout and T1 structural, finger movements motor task, self-perspective empathy training block, other-perspective empathy training block, and resting state; see Figure 2). The participant sat on the scanner bed and received several pulses of single-pulse TMS on the left primary motor cortex to determine her active motor threshold, informing the stimulation intensity for the cTBS on either the vertex or rSMG site (for details, see section TMS protocol). Immediately following cTBS, the participant entered the scanner for about 45 min, during which six 8-minute runs of MRI images were collected (scout/head localizer,

visuotactile empathy task runs 1 and 2, resting state run 1, task runs 3 and 4, resting state run 2). As the participant exited the scanner room, she filled in a survey about how she felt during and after cTBS and MRI ostensibly simultaneously as the confederate student. The participant and confederate were debriefed and left the facility together. The second day of testing took place one week later and was identical to the first day except that the pre-cTBS MRI session included a diffusion tensor imaging run instead of the T1, and that the motor task was removed. At the end of her second session, the participant received the participation fee and a full debriefing disclosing the goal of the study and the deception that had to be used to this end.

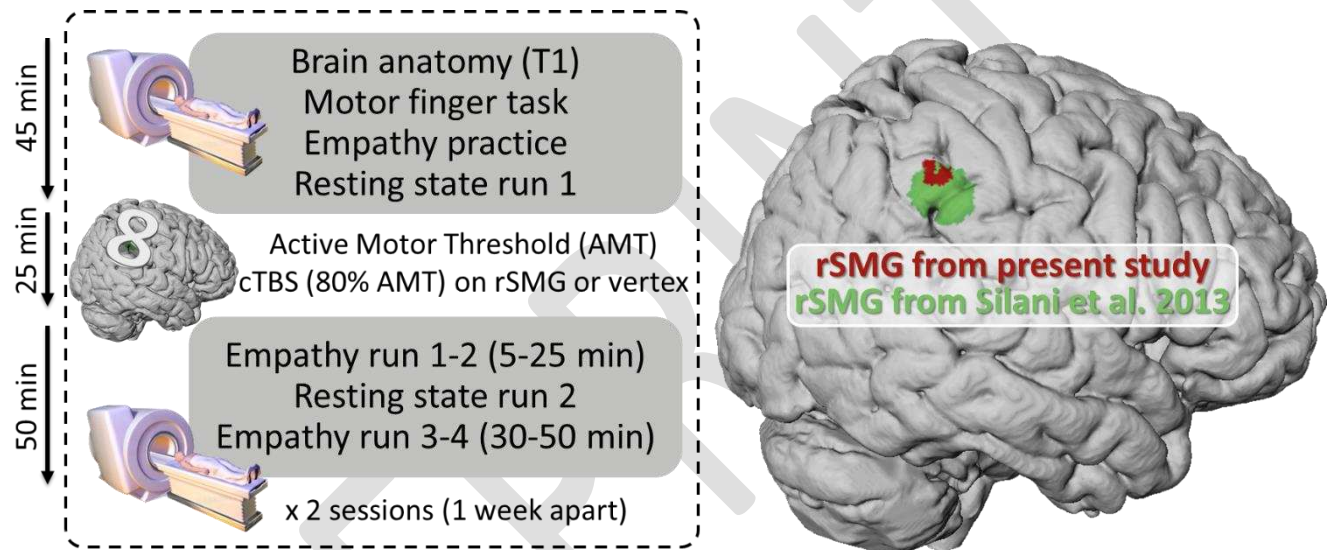


Figure 2. Neuroimaging methods and results: *Left panel:* Session 1 timeline. Steps in grey shaded boxes occurred in the scanner, with participants undergoing fMRI. Order of cTBS site was counter-balanced across participants. *Right panel:* Overlap of rSMG clusters found in Silani et al. (2013) and the present study (SVC-FWE $p < .05$).

2.3.1. Screening:

Each participant completed a standard medical screening questionnaire to screen for exclusion criteria for MRI and TMS (e.g., current or previous neurological or psychiatric abnormalities, drug or alcohol abuse, previous neurosurgery, current pregnancy, presence of metallic parts inside or on body that cannot be removed). Only participants satisfying all inclusion criteria were included in this study. Participants completed the German version of the QCAE. The QCAE has 31 items which are rated on a 4-point Likert scale ranging from 1 ('strongly disagree') to 4 ('strongly agree') and are divided into the Cognitive and Affective empathy subscales. The cognitive empathy subscale assesses essentially either the tendency to consider both perspectives in everyday life situations (e.g., "I always try to consider the other fellow's feelings before I do

something”) or the capacity to understand and predict others’ feelings (e.g., “Other people tell me I am good at understanding how they are feeling and what they are thinking”). Hence, this subscale was considered as the most adequate measure of dispositional empathic understanding, that is the capacity to reach understanding by (1) distinguishing our own emotions from another person’s and (2) flexibly modulating these emotions to accurately adopt a specific perspective (Coll et al., 2017; Decety & Meyer, 2008; Heyes, 2018).

2.3.2. TMS protocol:

In order to guide identification of the participant’s primary motor cortex representation of their right first dorsal interosseous (FDI), the participant completed a finger movement task in the scanner displaying a series of 10 sec of rest and 10 sec during which she alternately pressed her right index and middle finger on her thumb. Via a fast-automatized routine the fMRI data were directly analyzed (by contrasting finger movement and resting periods) to localize the left primary motor cortex (M1) upon the participant’s structural image with Brainsight 2 (Rogue Research Inc., Canada).

The TMS-coil, an MRi-B91 Butterfly Coil (MagVenture, Farum, Denmark) was manually positioned over the left M1 to determine the active motor threshold (AMT). Specifically, the participant pressed a foam earplug between their right thumb and index-finger with about 25% of her maximal strength while we stimulated 9 equally-spaced sites over M1 with single TMS pulses of identical intensity (40% of maximal stimulator output). TMS pulses were delivered by a MagPro R100 stimulator (MagVenture, Farum, Denmark) and concomitant FDI muscle contractions were assessed with motor evoked potentials (MEPs), recorded via adhesive electromyographic electrodes placed at the two ends of the muscle. The M1 site with highest MEP response received further TMS pulses with gradual increases of 5% until the MEP peak amplitude exceeded 0.5 mV. The intensity was then gradually reduced by 1% until only 3 out of 5 pulses of same intensity elicited a MEP responses exceeding 0.5 mV. The mean AMT for all participants was 58.16% (SD = 7.462%), and this value did not differ between the rSMG and vertex stimulation sessions ($t(30) = -0.192, p = .849$).

Once the AMT was determined, participants changed their seat and already sat down on the bed of the MRI-scanner in order to minimize the time interval between rTMS and completion of the empathy task. The participants sat still for approximately 10 min until the TMS equipment was

moved near the bed and the coil was properly positioned as indicated by the neuronavigation system. rTMS followed a continuous theta burst protocol, which consisted in a 40 secs train of stimulations during which three pulses were delivered at a rate of 50 Hz, every 200 ms (600 pulses in total). The intensity of stimulator output was set to 80% of each participants' individual AMT, as recommended by safety guidelines (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). The rSMG site of stimulation was defined by transforming the MNI coordinates of rSMG from Silani et al. (2013; fMRI study 2) into the participant's structural native space. If the transformation was somewhat inaccurate (different gyrus or outside grey matter), the nearest cortical site in the actual rSMG was defined manually by a trained researcher (for about a third of the participants). The vertex site was defined manually (meeting point of right and left central sulci in the interhemispheric fissure). The TMS coil was held in place manually and positioned over these sites tangentially to the cortical surface with the handle pointing 45° coronal-to-posterior and posterior for rSMG and vertex sites, respectively. No clinical incident occurred during or following the cTBS.

2.4. Visuo-tactile empathy task:

Completion of the visuo-tactile empathy task, developed by Silani et al. (2013), required to pair the participant with a female confederate, who ostensibly performed the same tasks simultaneously in an adjacent MRI scanning room. The central feature of the paradigm is that (1) the participant receives visuo-tactile stimulations eliciting either disgust or pleasantness while she sees what visuo-tactile stimulations her colleague receives at the same time, and then (2) she rates how intensely pleasant or unpleasant the emotional experience is for either herself or her colleague. The participant is instructed which perspective to take at beginning of each block of trials to either to focus and rate only their own visuo-tactile experience in "*Self-perspective*" blocks or to focus and rate only the imagined visuo-tactile experience of her colleague in "*Other-perspective*" blocks. Importantly, the *congruency* of the visuo-tactile experiences between the participant (the empathizer) and the confederate colleague (the empathized) was experimentally manipulated across trials: Emotional experiences could be both pleasant or both unpleasant, hence congruent, or of opposite valence, hence, incongruent. The task has a 2 (Congruency: congruent vs. incongruent) x 2 (Perspective: Self vs. Other) design where a congruency effect, that is a difference

between ratings in incongruent and congruent trials, reflects a failure to fully implement self-other distinction (see Figure 1).

The participant completed the empathy task while lying in the scanner, with a button-box in her right hand, a set of mirrors aligned with her eyes to view a screen back-projected from a projector, and her left hand lying palm up at the opening of the scanner bore. After oral and written instructions on the screen reminding the participant which perspective to take for the coming block of trials, each trial consisted of a fixation cross of jittered duration (mean: 3825 ms, range: 1800-5850 ms), followed by two pictures presented side by side (twice 400 x 400 pixels), surrounded by bounding boxes in different colors, and titled with the captions “Sie” and “Ihre Kollegin” (i.e., “You” and “Your colleague”, respectively) to indicate who (i.e., the participant or the confederate) experiences which visuo-tactile emotional experience. The pictures were displayed for 3 s and depicted a pleasant or unpleasant object (e.g., a pompom or a slug), while the participant was being simultaneously touched by a material creating the tactile experience corresponding to the object displayed by the picture under the “Self” caption (See Figure 1 panel A). Actual or fake materials were used depending on feasibility and compliance to hygiene standards (cf. Table A.1 in Appendices for the full list of visually presented objects and their corresponding tactile materials). The participant thus received the tactile stimulation corresponding to the picture under the “Self” caption (see Figure 1 panel A). After the 3 s of visual display accompanied by 3 strokes (i.e., at 1 Hz) by the corresponding material, participants were given a 4.5 s time window to rate the (un)pleasantness of the instructed visuo-tactile experience on a horizontal visual analog scale where the left-end displayed a face expressing strong disgust and the right-end displayed a face expressing strong enjoyment (see Figure 1, panel B). Responses were recorded via an MRI-compatible button box manipulated with three right-hand fingers to move a black star cursor left- or right-ward along the scale and to confirm the response (which changed the cursor’s color to red). The cursor was displayed at center of the scale at the outset of each rating trial and could be moved 4 times in either horizontal direction to indicate the level of perceived unpleasantness (left-ward) or pleasantness (right-ward). Hence, recorded ratings were discrete and ranged from -4 (*very unpleasant*) to +4 (*very pleasant*).

Each block lasted eight min and contained 20 pleasant trials and 20 unpleasant trials, presented in pseudorandom order so that valence, perspective, or congruency was never identical for more than three consecutive trials. Participants completed two Self-perspective blocks and two

Other-perspective blocks in each session directly after application of the cTBS protocol. To avoid habituation due to repeated exposure to the same visuo-tactile stimuli, we created four different sets of 20 stimuli (10 pleasant, 10 unpleasant), instead of one in the original paradigm. The stimuli had been selected from a larger set of 118 stimuli pretested by 24 female participants to select only stimuli specifically inducing pleasant or unpleasant affect (see Table A.1 for the list of stimuli).

Prior to the cTBS protocol, participants completed two fMRI runs in which only a single picture at a time was displayed centred on the screen, and participants either had to evaluate how the visuo-tactile stimulation felt to themselves, or, in a second block, to the other participant. Besides gaining some experience with the task paradigm and delivering the ratings, the first run allowed participants to experience from a first-hand perspective how each individual stimulus felt. This had been considered as essential in previous use of the paradigm in order to appropriately rate how stimulation would feel to another person (Riva, Tricoli, Lamm, Carnaghi, & Silani, 2016; Silani et al., 2013).

2.5. Behavioral analyses:

In line with our previous analysis approach (Riva et al., 2016; Silani et al., 2013), ratings in all unpleasant trials, where negative ratings were expected, were multiplied by -1 to allow analyses of emotion intensity that were independent of the valence of trials. The analysed and reported ratings therefore ranged from 0 (neutral) to 4, for both pleasant or unpleasant conditions, and their averages.

A repeated-measures ANOVA was conducted on these ratings of emotional intensity with Congruency (Congruent vs. Incongruent emotions conditions), Perspective (Self-perspective vs. Other-perspective conditions), cTBS site (rSMG vs. Vertex), and Time post-cTBS (T1 [5-25 min] vs. T2: [30-50 min]) as within-subject (repeated-measures) factors. Besides this omnibus analysis approach, we performed planned contrasts to test central hypotheses formulated *a priori*. These targeted the extent of reduction in ratings between Incongruent and Congruent trials – the congruency effect, as an indication of the extent of bias in participants' judgements and thus the extent of self-other distinction difficulties. Since our main intention was to first identify these difficulties and then to find an effect of cTBS, a first planned comparison assessed the difference in ratings on congruent and incongruent trials, while a second planned comparison assessed whether these differences differed between sites of stimulation (i.e., rSMG vs. Vertex). In a subsequent *post-hoc* analysis, motivated by our findings (see below), the cognitive empathy

subscale of QCAE was entered as a continuous between-subject variable to assess dispositional empathic understanding in relation to the congruency effect. Given the small sample size to conduct correlations, 95% confidence intervals were calculated via a 1,000 iterations bootstrap procedure (bias corrected and accelerated) in order to be able to address potential concerns that particular data points would drive the observed relationship. At last, comparisons between correlations were tested according to Lenhard and Lenhard (2014).

2.6. MRI data acquisition and analyses

Structural T1 and functional T2*-weighted images were acquired using a whole-body Siemens 3 Tesla Tim Trio whole body magnet, and a 32-channel head coil (Siemens Medical, Germany). The structural image sequence acquired 160 slices of 1.1 mm thickness (50% slice gap) parallel to the AC-PC-plane with a 1 x 1 mm in-plane resolution (256 x 256 matrix; slice TE/TR = 4.21/2300 ms). Functional data acquired immediately after the cTBS protocol consisted of 6 runs of 8 mins (807 volumes) with identical parameters: 2 empathy blocks, one resting-state block (not analyzed here), 2 empathy blocks, and one resting-state block (not analyzed here). Each volume comprised 21 descending interleaved slices of 4 mm thickness (25% slice gap) parallel to the AC-PC-plane with a 2 x 2 mm in-plane resolution (96 x 96 matrix; TE/TR = 35/600 ms ; multi-band accelerator factor = 3). All MRI data were processed and analyzed using SPM12 (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm).

The fMRI time series were analyzed using an event-related design by setting up general linear models with multiple regressors in SPM12. The stimulation period (3 s) as well as the rating window (4.5 s) were modeled as distinct event-related regressors, and the inter-trial fixation cross (jittered duration) served as the implicit baseline. More specifically, single-subject (first-level) models consisted of multiple regressors separately modeling all possible combinations of Congruency (Congruent vs. Incongruent emotions conditions), Perspective (Self-perspective vs. Other-perspective conditions) and Time post-cTBS (T1 [5-25 min] vs. T2: [30-50 min]). Each effect was modeled as a boxcar function, and then convolved with SPM12's canonical hemodynamic response function. Residual head movement effects were accounted for by including the six rigid-body motion parameters (translation and rotation) as nuisance regressors. Like in the behavioral analyses, our two main planned contrasts compared the Congruent and Incongruent trials and their interaction with site of cTBS (rSMG vs. Vertex). These first-level contrasts were entered into a second/group-level fixed-effects analysis. Also in line with the behavioral analyses

and results, a third contrast evaluated the impact of individual differences in self-reported empathic understanding on the Congruency x cTBS-site interaction, based on the multiple regression function in SPM12 (with questionnaire scores and the first-level interaction contrast entered as covariates).

Based on consistent findings of rSMG recruitment in empathy-related self-other distinction (Silani et al., 2013; Steinbeis et al., 2015), we first inspected the results of these contrasts in the rSMG using a small volume correction (SVC, $p < .05$ corrected for family-wise error (FWE)) approach. The region of interest (ROI) for SVC had been derived from previous research using the same task, and consisted of the cluster in rSMG identified by fMRI study 2 in Silani et al., 2013 (centered at $x=68$, $y=-38$, $z=36$, and containing 152 $2 \times 2 \times 2$ mm voxels). These analyses targeting *a priori* hypotheses about rSMG involvement were complemented by whole-brain analyses thresholded at $p < .05$ FWE voxel-level correction, as well as with uncorrected $p < .001$. The latter represents an exploratory analysis approach, with the aim to reduce the risk of false negatives if the former threshold revealed no significant activities; naturally, this approach provides no strict control over the false positive rate, and thus needs to be considered with caution

In line with behavioral findings, we also conducted post-hoc analyses looking at how individual differences in dispositional empathic understanding relates to the brain activations for the Congruency x cTBS site interaction in the ROI rSMG, individually defined rSMG (see below) and whole-brain. A liberal threshold of uncorrected $p < .005$ ($k > 5$ voxels cluster) was additionally adopted to explore for each network how it was positively or negatively correlated with self-reported empathic understanding. Note that these analyses were exploratory and did not provide strict control of the false positive rate either.

Finally, we noticed considerable heterogeneity regarding the anatomical location of rSMG across individuals. To alleviate the effects this might have had on brain activation, we extracted the mean beta-values for the planned Congruency by cTBS site interaction contrast (rSMG > vertex: Incongruent > Congruent emotions conditions) of the voxels contained in a 10 mm-diameter sphere centered on each participant's manually-determined rSMG stimulation site. This data was entered in a correlation analysis with each participant's dispositional empathic understanding.

3. Results

3.1. Behavioural results:

The repeated-measures ANOVA of the ratings revealed a significant main effect of Congruency $F(1,30) = 7.118, p = .012, \eta_p^2 = .192$, with a lower mean emotional intensity in the incongruent emotions condition, a marginally significant main effect of Time, $F(1,30) = 4.005, p = .054, \eta_p^2 = .118$, with a lower mean emotional intensity in the T2 (30-50 min post cTBS) condition, a marginally significant Congruency x Time interaction, $F(1,30) = 3.880, p = .058, \eta^2 = .115$, with a lower Congruency effect in the T2 condition, and a marginally significant Congruency x cTBS site interaction, $F(1,30) = 3.564, p = .069, \eta_p^2 = .106$, with a lower Congruency effect (i.e., lower self-other distinction bias) in the rSMG condition ($M_D = 0.020, SD_D = 0.108, t(30) = 1.047, p = .304$) than the vertex condition ($M_D = 0.069, SD_D = 0.125, t(30) = 3.047, p = .005$; see also Figure B.1 in Appendices). All other effects were non-significant (all $F_s > 1.670, p_s > .205$). It is noteworthy that the Congruency x Perspective interaction was non-significant and of very low effect size, $F(1,30) = 0.077, p = .783, \eta_p^2 = .003$ (including in the vertex condition, $F(1,30) = 0.237, p = .630, \eta_p^2 = .003$; see Figure 1), meaning that the congruency effect when judging the other person's emotion (i.e., the egocentric bias; $M_D = 0.048, SD_D = 0.133$) and the congruency effect when judging one's own emotion (i.e., the altercentric bias; $M_D = 0.041, SD_D = 0.103$) did not seem to differ.

Unexpectedly and against our main hypothesis, the marginally significant Congruency x cTBS site interaction shows that cTBS did not disrupt self-other distinction performance, but rather tended to enhance it, on average (i.e., in the whole sample). Aiming to explain this result, we explored the *post-hoc* hypothesis that individual differences on an independent measure of baseline empathic understanding (which is closely related to self-other distinction) predicted the direction of the rTMS effects (see Discussion for arguments of Paracampo et al., 2018 for a similar hypothesis). We thus ran the same ANOVA as before except that it included as a covariate participants' dispositional empathic understanding (measured by their scores on the Cognitive Empathy subscale of the QCAE (Reniers et al., 2011)). The analysis revealed a significant Congruency x cTBS site interaction, $F(1,29) = 11.658, p = .002, \eta_p^2 = .287$, and a significant Congruency x cTBS site x Empathic understanding interaction, $F(1,29) = 10.346, p = .003, \eta_p^2 = .263$. All other effects were non-significant (all $F_s > 2.093, p_s > .158$).

To unravel the Congruency x cTBS site x Empathic understanding interaction, we first sought to inspect the correlations between dispositional empathic understanding and the different biases “at baseline”, meaning in the absence of rSMG stimulation (and thus in the vertex condition);

then we tested how empathic dispositions correlated with the direction of the cTBS effect when rSMG was stimulated. Higher dispositional empathic understanding was negatively correlated with the Congruency effect in the Vertex condition to a marginally significant extent, $r(31) = -.351, p = 0.053$ (95% bootstrapped CI: $-.590$ to $-.038$). When examining whether empathic understanding relates to both the egocentric and altercentric biases in vertex session, we found that both biases are negatively correlated with empathic understanding, $r(31) = -.204, p = 0.272$ (95% bootstrapped CI: $-.484$ to $.225$) for egocentric bias, $r(31) = -.390, p = 0.030$ (95% bootstrapped CI: $-.627$ to $-.043$) for altercentric bias, and that the two correlations do not differ statistically, $z = -0.848, p = .200$, although the correlation is significant only for the altercentric bias. Together these correlations indicate that at baseline, individuals scoring higher on dispositional empathic understanding have lower biases¹, and thus better self-other distinction performance, and that the altercentric bias is as well relevant to empathic understanding.

We then inspected how the difference of Congruency effects between the two cTBS sessions (i.e., (rSMG: Congruent – Incongruent) – (vertex: Congruent – Incongruent)) is associated with dispositional empathic understanding, which was found to be significant, $r(31) = .513, p = 0.003$ (95% bootstrapped CI: $.233$ -.701). This correlation, depicted in Figure 3 (upper panel), indicates that participants with lower dispositional empathic understanding had a lower Congruency effect (i.e., smaller self-other distinction bias) following rSMG compared to vertex cTBS, while this relationship was reversed (i.e., higher self-other distinction bias) in participants with higher dispositional empathic understanding (see also Figure B.2 for a bar plot version based a median split between low and high dispositional empathic understanding). In other words, cTBS of the rSMG enhanced self-other distinction performance the more that individuals showed poor dispositional empathic understanding.

¹ Correlation between Congruency bias and empathic understanding in rSMG session significantly differ from the correlation in vertex session; see Figure B.3 in Appendices.

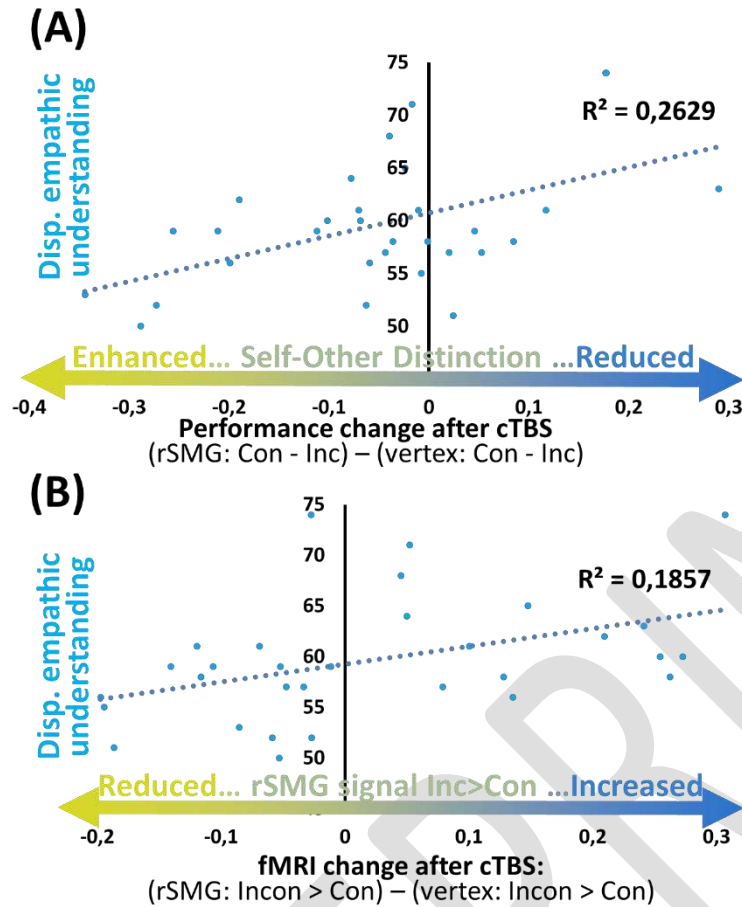


Figure 3. Dispositional empathic understanding significantly correlates with the effects of cTBS on how incongruent self-other emotions are processed in comparison to when emotions are congruent. (A): cTBS of the rSMG enhanced self-other distinction performance (i.e., lower Congruency effect or bias in ratings) the more that individuals showed poor dispositional empathic understanding, or reduced performance (i.e., higher bias) the more they showed high disposition. In short, participants with lower dispositional empathy got better at self-other distinction whereas participants with higher empathy got worse. (B): cTBS of the rSMG reduced the extent to which rSMG is more active for Incongruent than Congruent trials (in comparison to vertex baseline) the more that individuals showed poor dispositional empathic understanding, or increased rSMG activation the more they showed high disposition. In short, after cTBS of rSMG compared to vertex, participants with empathy activated rSMG less during incongruent self-other emotion trials, and vice versa.

3.2. fMRI results:

Our planned comparisons had foreseen to test the main effect of Congruency (Incongruent vs. Congruent trials) and its comparison between cTBS sites (rSMG:Inc>Con vs. vertex: Inc>Con) in the rSMG ROI derived from Silani et al. (2013) and in the whole-brain space. The Congruency contrast conducted in the rSMG ROI from Silani et al. (2013) revealed significantly higher activation related to incongruent trials (SVC-FWE-corrected $p < .05$). While the complementary

whole brain analysis ($p < .05$ voxel-level FWE-corrected across the whole brain) did not reveal additional activation in other parts of the brain, the more liberal threshold of $p < .001$ (uncorrected) indicated additional activation in the bilateral mid-anterior insula, bilateral occipital cortex along the calcarine fissure, and the right SMG (overlapping with the ROI used in the SVC analysis; see Table 1). These findings conceptually replicate the involvement of the right SMG in self-other distinction in empathy, and suggest a complementary role of additional areas involved in affective and visual processing.

The Congruency \times cTBS site interaction revealed no significant clusters, neither for the ROI analysis of rSMG, nor the whole brain analyses (at $p < .05$ FWE-corrected, and $p < .001$ uncorrected). Thus, in line with the behavioural results, no group-level effects of rSMG-cTBS on self-other distinction were found.

Following up on the individual-difference analysis of the behavioural data, we then also explored how individual differences in empathic understanding correlated with rSMG activation during self-other distinction at baseline (i.e., in vertex), and then how this changes from the vertex to rSMG cTBS sessions. The extent to which the rSMG was more active in Incongruent trials (i.e., when self-other distinction is required to prevent biases) than in Congruent trials in the vertex session was significantly and negatively correlated with dispositional empathic understanding, $r(31) = -.356$, $p = 0.049$ (95% bootstrapped CI: $-.613$ to $-.085$)². This indicates that, at baseline, individuals scoring higher on dispositional empathic understanding activated less the rSMG during incongruent than congruent trials, and vice versa. We then inspected how the differences in activation between Incongruent and Congruent trials, across the two cTBS sessions (i.e., (rSMG: Incongruent – Congruent) – (vertex: Incongruent – Congruent)), is correlated with dispositional empathic understanding. The correlation was found significant in the individually delineated rSMG stimulation sites, $r(31) = .431$, $p = .015$ (95% bootstrapped CI: $.154$ - $.677$; see Figure 3, right panel), but not in the rSMG ROI from Silani et al. (2013)). This association mirrors the one found at the behavioural level (see Figure 3), suggesting that the improvement of self-other distinction in participants with lower dispositional empathic understanding when stimulating their rSMG is associated with diminished activation in their rSMG during self-other distinction. However, examination of the direct association between rSMG activation changes and self-other distinction

² Correlation between rSMG activation for Inc>Con and empathic understanding in rSMG session significantly differ from the correlation in vertex session; see Figure B.3 in Appendices.

performance changes across the two cTBS session yielded a non-significant correlation, $r(31) = .202$, $p = .277$ (95% bootstrapped CI: $-.112$ to $.460$).

Aiming to further explore the interaction cTBS-site x Congruency x empathic understanding, we looked for the same association as the one for rSMG activation, but in the whole-brain space. No cluster was positively or negatively correlated to empathic understanding at $p < .05$ voxel-level FWE-corrected across the whole brain. In order to avoid risks of false negatives (Lieberman & Cunningham, 2009) and because we expected maximal and realistic brain-questionnaire correlation coefficients to be around $r = 0.6$ (based on the central tendency of published brain-behavior correlation coefficients in Vul, Harris, Winkielman, & Pashler, 2009) and thus maximal p-values for our sample size ($N=31$) to be around $.003$ (calculated with GPower 3.1 with default power of $.80$), we additionally assessed correlations at the exploratory threshold of $p < .005$ uncorrected. At that threshold, the middle insula bilaterally, the anterior part of the middle cingulate cortex (aMCC) bilaterally, the primary somatosensory area and premotor cortex corresponding to the hand/finger somatotopy showed a positive correlation (see Figure 4 and Table 1). Note that if a brain region whose activation pattern resulting from the cTBS x Congruency contrast is positively associated with dispositional empathic understanding, this region becomes more active during self-other distinction (Incongruent > Congruent trials) following cTBS on rSMG (in comparison to cTBS on vertex site) among individuals scoring *higher* in dispositional empathic understanding. In short, cTBS of the rSMG increased activation within a sensory-affective network during trials prone to self-other distinction biases the more that individuals showed high dispositional empathic understanding. The negatively correlating areas were the right posterior parietal cortex (dorsal angular gyrus and posterior intra-parietal sulcus) and the lateral orbitofrontal cortex bilaterally, extending in the right anterior dorsolateral prefrontal cortex (see Figure 4 and Table 1). In other words, cTBS of the rSMG increased activation within a fronto-parietal network during trials prone to self-other distinction biases the more that individuals showed poor dispositional empathic understanding.

These findings, though exploratory in the sense that we do not have family-wise control over the false positive rate, point towards the possibility that two distinct networks are engaged during self-other distinction after cTBS on rSMG, and that this depends on whether participants showed low or high dispositional empathic understanding.

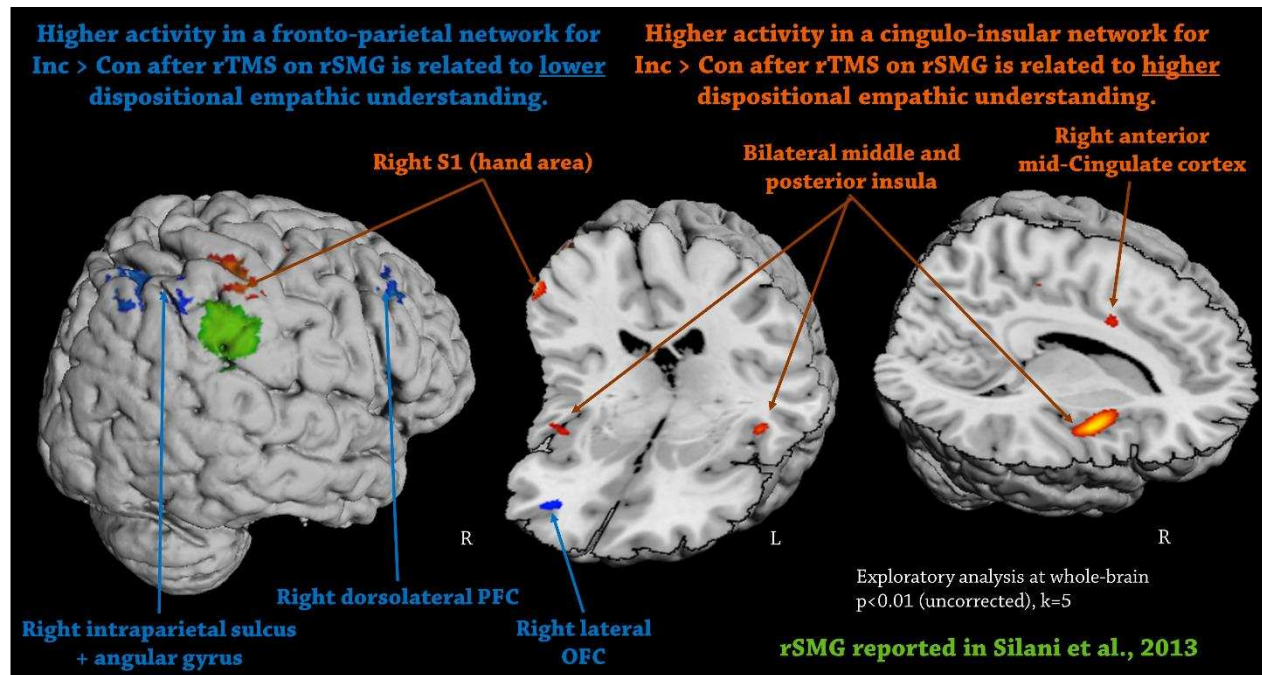


Figure 4. fMRI results of the triple interaction between Congruency effect, cTBS site, and dispositional empathic understanding. Lower empathic understanding is associated with increased engagement of a “cognitive control” network during incongruent trials, after cTBS on the rSMG (rSMG (Inc>Con) > vertex (Inc>Con)). Higher dispositional empathy, on the other hand, recruits an “affect sharing” network for the same contrast.

Table 1. fMRI results

Incongruent > Congruent – ROI SVC-FWE $p < .05$					
	Cluster size (m^3)	x	y	z	Z scores
Right supramarginal gyrus	192	64	-36	40	3,26
Incongruent > Congruent - uncorrected $p < .001$					
	Cluster size (m^3)	x	y	z	Z scores
Left middle insula	608	-44	0	4	3,61
		-42	8	-8	3,46
Right middle insula	448	44	8	-8	3,74
Right occipital cortex / cuneus lobe	784	18	-90	4	4,04
Left occipital cortex / cuneus lobe	624	-20	-94	8	3,86
Right supramarginal gyrus	80	64	-36	40	3,26
Covariate Empathic Understanding * (Inc > Con: cTBS rSMG > Vertex) – uncorr. $p < .005$, $k \geq 5$					
	Cluster size (m^3)	x	y	z	Z scores
(+) Right middle insula	1472	40	4	8	3,31
		48	4	-12	2,74

SELF-OTHER DISTINCTION RTMS/FMRI

(+) Right primary somatosensory cortex (fingers)	848	62	-22	44	3,05
		54	-28	56	3,01
(+) Left ventral posterior insula	224	-46	-8	-8	3,02
(+) Right ant. middle cingulate cortex	208	14	8	36	2,99
(+) Left ant. middle cingulate cortex	432	-8	18	32	2,88
(+) Right premotor cortex (fingers)	112	42	-8	60	2,70
(-) Right posterior IPS / dorsal angular gyrus	1072	42	-62	56	3,40
(-) Right anterior dlPFC / lateral OFC	752	40	54	-4	3,07
		32	48	-4	3,00
(-) Left lateral OFC	80	-30	40	-4	2,85

Notes: ROI = region of interest; SVC = small volume correction; FWE = family-wise error correction; (+) = positive association; (-) = negative association; IPS = intra-parietal sulcus; dlPFC = dorsolateral prefrontal; OFC = orbitofrontal.

4. Discussion

Empathy necessitates self-other distinction to tease apart self-experienced emotions and those experienced by others (de Vignemont & Singer, 2006; Decety & Meyer, 2008; Lamm et al., 2016). When there is a discrepancy between self- and other-experienced emotions (such as when one person is feeling disgusted, while the other is pleased), failure to fully implement self-other distinction translates at the behavioral level into altercentric and egocentric biases in the interpretation of self- and other-related emotional states, respectively (Silani et al., 2013). At the neural level, the right supramarginal gyrus (rSMG) has been found more active in situations where self- and other-related emotions are incongruent than when they are congruent (Silani et al., 2013; Steinbeis et al., 2015), and rTMS disruption of this area caused a substantial increase in egocentric bias (Silani et al., 2013). The present study aimed to extend our understanding of the role of the rSMG in self-other distinction by measuring self-other distinction performance and its fMRI neural correlates following rTMS on the rSMG and the vertex across two sessions completed by the same 31 female participants.

Our main results confirmed that participants overall were biased in their judgements, reflecting a failure to fully enforce affective self-other distinction, and this was accompanied by higher fMRI activation during incongruent than congruent self-other emotions trials. However, comparison of performance and fMRI activity of self-other distinction between the rSMG-cTBS session and the vertex-cTBS session (control site condition) revealed no consistent effects of rTMS across the whole sample. With these planned analyses having resulted in no significant results, we explored the potential role of individual differences in self-reported dispositional empathic understanding. This which uncovered several findings, whose implications are discussed now, followed by a discussion of their limitations, due to their explorative nature.

Empathic understanding significantly correlated with self-other distinction bias and rSMG activation in trials prone to biases at baseline and correlated particularly with how rTMS differentially affected the bias and the rSMG activation. Specifically, lower empathic understanding was associated with less bias and less active rSMG in incongruent emotions trials after rTMS on rSMG (in comparison to bias and the extent the rSMG is more active in incongruent than congruent trials after rTMS on the vertex), while rTMS induced more bias and more activity in participants with a higher disposition for empathic understanding. Exploring correlations beyond

the rSMG, lower disposition was associated with more activity in the posterior parietal cortex (dorsal angular gyrus and posterior intra-parietal sulcus), the lateral orbitofrontal cortex bilaterally, and the right anterior dorsolateral prefrontal cortex, whereas higher empathic understanding was associated with more activity in the middle insula bilaterally, the anterior midcingulate cortex, and the left hand's somatosensory-motor areas.

Failure to fully enforce self-other distinction is commonplace even among healthy adults, whose social judgements are egocentrically biased by their own inner states, or altercentrically biased by others' inner states. This has been largely demonstrated for non-affective mental states, such as visual perspectives (Samson et al., 2010) and beliefs (Birch & Bloom, 2007), and overcoming such biases is considered essential in Theory of Mind and perspective taking tasks (Royzman et al., 2003). The investigation of self-other distinction for emotions was only recently introduced to the literature, documenting similar egocentric and, to a lower extent, altercentric biases (Hoffmann et al., 2016, 2015; Riva et al., 2016; Silani et al., 2013; Steinbeis et al., 2015; Tomova et al., 2014; von Mohr et al., 2019). In the present study, we found that participants could not completely ignore neither their own conflicting emotion nor the other person's conflicting emotion when judging how her colleague felt or how she felt. The resulting egocentric and altercentric biases, which document *under*-estimations of the other's and one's own emotions, thus indicate a lack of empathic as well as of self-understanding due to a failure of fully enforcing self-other distinction.

Across both rTMS conditions, fMRI scanning while participants completed the visuo-tactile empathy task revealed higher activity for incongruent trials in the rSMG, within the same area reported in two previous fMRI studies investigating egocentric bias in empathy (Silani et al., 2013; Steinbeis et al., 2015). However, we did not find involvement of lateral prefrontal cortex, whose connectivity with the rSMG was shown to predict individual differences in participants' egocentric bias (Steinbeis et al., 2015). This suggests that at the group-level, self-other distinction was not consistently enforced via prefrontal top-down selection of the relevant emotional experience.

It has previously been argued that rSMG engagement reflects overcoming emotional egocentricity (Silani et al., 2013). How exactly this is achieved or implemented on the neural level remained unclear so far. Our findings shed new light and open up a slightly different angle on this

previous interpretation - which had been based on separately performed fMRI and TMS studies and thus was not able to quantify the exact effects TMS had on this area, and the networks it connects to. Building upon the knowledge that BOLD activation reflects mainly pre-synaptic activity (i.e., inputs rather than outputs) (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001), it seems plausible that the rSMG is more active in incongruent trials because two simultaneous distinct emotional experiences implies more sensory-affective inputs than two similar (but not exactly identical) emotional experiences in congruent trials. For incongruent trials, if one successfully enforces self-other distinction to select one perspective (i.e., one source of inputs) and suppresses the other, this would lead to the rSMG becoming less active than in congruent trials, since the latter condition contain two sources of inputs. This would also imply that increased activation in the rSMG reflects insufficient self-other distinction in the sense of a failure to select one emotional experience and inhibit the other. Further insights to test this interpretation could be gained by our study, in applying rTMS on the rSMG and assess subsequent performance and neural activity during self-other distinction.

We used a conventional continuous theta-burst stimulation (cTBS) protocol (introduced by Y. Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) to neuromodulate the rSMG and the vertex (a control cortical site where no functional impact of rTMS is expected) in two separate sessions, and a within-subject design. In comparison to cTBS of the vertex, rSMG stimulation did influence the extent of ego- and altercentric biases, but only to a marginal extent ($p = 0.069$), and in the direction of a *reduction* of biases with rSMG stimulation (effect size of bias in rSMG and vertex were $d = 0.19$ and $d = 0.55$, respectively). Based on previous cTBS studies (e.g., Di Lazzaro et al., 2005; Y. Huang et al., 2005; Zafar, Paulus, & Sommer, 2008) describing a predominantly inhibitory effect on motor performance, as well as our own previous findings of a decrease in self-other distinction following “inhibitory-disruptive” rTMS of rSMG, this was clearly unexpected. Rather, we had expected a general deterioration of self-other distinction performance following cTBS on the rSMG.

The unexpected null effect of cTBS led us to explore the role of individual differences in dispositional empathic understanding on the cTBS effects. Many recent studies and observations indicate significant individual differences regarding the behavioural and neurophysiological impacts of cTBS (e.g., Crescentini, Di Bucchianico, Fabbro, & Urgesi, 2015; Hamada, Murase,

Hasan, Balaratnam, & Rothwell, 2013; Hordacre et al., 2017; G. Huang & Mouraux, 2015; Jannati, Block, Oberman, Rotenberg, & Pascual-Leone, 2017; McAllister et al., 2013; Palmer, Bunday, Davare, & Kilner, 2016; Sasaki et al., 2017; Valchev, Gazzola, Avenanti, & Keysers, 2016; Valchev, Tidoni, Hamilton, Gazzola, & Avenanti, 2017), including in self-other distinction in Theory of Mind (Hartwright, Hardwick, Apperly, & Hansen, 2016; Krall et al., 2016). This research focus on individual difference in TMS effects has mainly been emerging from studies examining the neurophysiological and genetic predictors, but psychological factors such as attentional focus have also been reported (for reviews, see Chung, Hill, Rogasch, Hoy, & Fitzgerald, 2016; Y. Z. Huang et al., 2017; Ridding & Ziemann, 2010). A research finding that is particularly noteworthy in the present context is the one of Paracampo et al. (Paracampo et al., 2018). These authors found individual differences in baseline empathic accuracy to be a significant predictor of the variable effects rTMS on the TPJ had on empathic accuracy. In their study, higher empathy was associated with a negative impact of rTMS on performance. This fits our own data, which indicate that rTMS of rSMG in participants with higher empathic understanding led to an increase in biases and thus a decrease in empathic understanding.

More specifically, individual differences in empathic understanding significantly explained the variance in how rTMS on rSMG impacted on self-other distinction performance and neural activity. Higher dispositional empathic understanding was associated with (1) a deteriorating impact of rTMS on self-other distinction performance (i.e., less accurate empathic understanding, which is in line with Paracampo et al. (2018)) and increased activations for incongruent trials in (2) the individually defined rSMG and (3) an affective sensori-motor network, corresponding to the affect sharing network, comprising the somatosensory and premotor areas corresponding to the hand area stimulated, and the bilateral middle insula with the anterior middle cingulate cortex (for recent reviews, see Keysers, Kaas, & Gazzola, 2010; Riečanský & Lamm, 2019). Conversely, lower empathic understanding was associated with (4) enhanced self-other distinction performance with rTMS of rSMG, (5) reduced activations for incongruent trials in the individually defined rSMG, and (6) increased activations for incongruent trials in a fronto-parietal network comprising the right posterior parietal cortex (dorsal angular gyrus and posterior intra-parietal sulcus), and the right anterior dorsolateral prefrontal cortex along with the lateral orbitofrontal cortex, bilaterally (see Figure 4). The concomitant findings (1-3) supports the above-mentioned interpretation that higher activation in incongruent trials might reflect a failure to fully implement self-other

distinction with a neural network signature corresponding to the affect sharing network. In contrast, findings (4)-(6) support the interpretation that cognitive control is required to successfully enforce self-other distinction (Hoffmann et al., 2015; Lamm et al., 2016; Steinbeis et al., 2015), and that lower activation in incongruent trials might reflect the reduction of ascending inputs caused by the selection of a single emotional perspective. To be explicit, these interpretations are not supported by a statistically significant association between rSMG activation and self-other distinction performance but by both variables being significantly correlated with dispositional empathic understanding.

Against this background of results, we would now like to discuss what exact role the rSMG may play during self-other distinction, and how our findings advance that knowledge. While previous neuroimaging studies (Silani et al., 2013; Steinbeis et al., 2015) of self-other distinction in empathy have argued that the rSMG is necessary to enforce self-other distinction, our findings suggest that activity in the rSMG does not necessarily imply that self-other distinction is enforced. Based on the present findings, we would argue that the rSMG is a cortical associative area and thus, per definition, a node where ascending inputs converge and through which prefrontal top-down selection is enforced on posterior upstream cortices (Mesulam, 1998). Hence, our results suggest that the rSMG is necessary to enforce self-other distinction via top-down selection (as in Silani et al., 2013 in their rTMS experiment), but its activation may merely reflect the extent of upstream convergence and not necessarily self-other distinction per se. The exact role of the rSMG is therefore specific to each individual and situation, and it can only be grasped by taking into account each individual's performance and dispositions to enforce self-other distinction. While outlining some plausible mechanisms, these interpretations are speculative and based on exploratory findings with uncorrected fMRI statistical thresholds and within an exclusively female sample. Future studies are thus needed to replicate and extend our findings, to test their generalization to the male population, and to more directly address the possible neural mechanisms by which rSMG achieves self-other distinction in empathy.

A question that remains to be addressed is how, on a neural and mechanistic level, the individual differences in dispositional empathic understanding could have influenced the impact of cTBS rTMS on self-other distinction. One potential explanation is based on the possibility that higher empathic understanding relates to stronger structural connectivity between the rSMG and

executive fronto-parietal areas whereas lower scores relate to stronger connectivity between the rSMG and the affect sharing network (i.e., the bilateral insula and anterior middle cingulate cortex, see e.g. Lamm et al., 2011, for meta-analysis). Brain stimulation thus affects these two networks in distinct ways and disrupts different computational capacities of the rSMG. As a result, high empathizers could have more difficulties to benefit from cognitive control resources to enforce self-other distinction after rTMS of the rSMG, whereas low empathizers' emotional experiences could become altered after rTMS, rendering them e.g. less integrated or less salient. Consistent with this hypothesis, Hartwright et al. (2016) found a deterioration of non-affective self-other distinction performance following rTMS on the right ventrolateral prefrontal cortex associated with stronger connectivity with right TPJ, and also with higher grey matter density in right TPJ itself. A second and complementary explanation would be that the rSMG itself is shaped by individuals' (lack of) self-other distinction habits or propensity (e.g. the propensity and frequency to engage in self-other distinction; see Keyzers & Gazzola (2014) on the distinction between propensity and ability of empathy in psychopathy). Upon rTMS, the rSMG's propensity to be engaged is neutralized, and this which would penalize self-other distinction performance of high dispositions individuals but become beneficial for low dispositions individuals. Relatedly Morishima et al. (Morishima, Schunk, Bruhin, Ruff, & Fehr, 2012) found that grey matter within the right TPJ predicts how selfishly an individual would behave in social decision making and how the right TPJ is activated during the task. At last, a third (and again complementary) explanation could be that dispositional empathic understanding affected baseline cortical activation of the rSMG, which is known to determine whether rTMS will facilitate or disrupt behavioural performance (Nicolo, Ptak, & Guggisberg, 2015; Silvanto, Cattaneo, Battelli, & Pascual-Leone, 2008). Specifically, induced long term depression is more likely than long term potentiation if the rSMG was highly activated at time of rTMS whereas low activation has the opposite effect. The rSMG was possibly more active among participants with high dispositions for empathic understanding because they were more likely to activate the rSMG as they were socially interacting with the researchers to follow their instructions or as they trained at rating the other person's feelings 20-30 min before cTBS. Relatedly, motor activity immediately prior or after cTBS influenced the rTMS impact in previous studies (Y. Z. Huang et al., 2017) and thus possibly the present study; this hypothesis can however be excluded because participants remained at rest for about 10 minutes prior cTBS. In conclusion, and irrespective of the way the individual differences translated at the brain level, it seems crucial

to note that these individual differences relates to a baseline state of empathic functioning. This is so because individual differences in self-reported empathic understanding were found to be correlated with self-other distinction performance and related rSMG activation also in the vertex condition, that is, at baseline.

Elucidating why and how rTMS impacts cognition differently across individuals is still far from clear given the novelty of the research field. While providing a final answer to this question is beyond the scope of our study, or any single study, that is, it is interesting to note that experimental manipulation of the synaptic history of the stimulated region predicts the rTMS impact (Ridding & Ziemann, 2010). Given recent developments in the field, it is only a matter of time before self-reported tendencies and capacities will be considered as synaptic history (for instance, see Yang, Khalifa, Lankappa, & Völm, 2018 for another study including the QCAE to predict rTMS effects).

Although an absence of inhibitory effects of cTBS is not surprising in regard of the reviewed literature, this finding stands in contrast to the inhibitory effect of 1-Hz rTMS on egocentricity in empathy reported by Silani et al. (2013). The cTBS and 1-Hz protocols are both intended to be inhibitory but current evidence and understanding point towards distinct neurophysiological pathways: 1-Hz rTMS reliably induces long-term depotentiation (LTD) and, for the motor cortex, is accompanied by facilitating effects on the contralateral non-stimulated areas whereas cTBS induces both LTD and long-term potentiation that less reliably results in inhibitory effects, and that, at least for the motor cortex, are similar on both hemispheres (Gilio, Rizzo, Siebner, & Rothwell, 2003; Y. Huang, Rothwell, Chen, Lu, & Chuang, 2011; Klomjai, Katz, & Lackmy-Vallée, 2015). In addition, direct comparisons of the 1-Hz and cTBS rTMS indicate that cTBS had weaker, more variable, or no inhibitory effects (Brückner, Kiefer, & Kammer, 2013; Nyffeler et al., 2006; Waterston & Pack, 2010). Hence, the non-replication of the inhibitory effect reported in Silani et al. (2013) may not be that surprising in regard of the reviewed literature. That being said, given the strong assumption that we would be able to replicate and extend the original findings using the cTBS protocol as well, our study remains somewhat agnostic to how the inhibitory effects in the original 1 Hz rTMS study impacted the brain and neural networks

associated with rSMG³. Future research should clarify the respective impacts of cTBS and 1 Hz rTMS on high-level cognition and not assume similar effects.

6. Conclusions

By combining fMRI and rTMS methods, we confirmed and suggest a novel interpretational angle for the role of the rSMG in self-other distinction. Our study in particular highlights the importance to consider the so far overlooked altercentric bias along with the egocentric bias to assess self-other distinction performance in empathy, and that the role of individual differences in how brain stimulation affects task performance and associated brain activations should be given more consideration. Our approach also confirms that triangulating behavioural phenomena by a mix of different methods may yield converging evidence, and thus paint a more clear and consistent picture on the neural and psychological underpinnings of self-other distinction, and empathy in general. Although exploratory and in need of replication, the finding that individual differences in traits or dispositions leads to converse effects of rTMS on performance and related brain activity nicely connects “psychology” and “neuroscience.” This might help to move toward more mechanistic insights considering the vast individual differences in both cognition, brain and behaviour that enrich but also complicate social interaction and behaviour in general.

³ Note that the mean Perspective Taking score as measured by the IRI (Davis, 1980) in the rTMS experiment in Silani et al. 2013 ($M = 18.24$) is similar to those in the low-empathic understanding group (defined by median split; $M = 18.28$); which suggests that the opposite rTMS effects between the two rTMS studies are not due to a sample difference in dispositional perspective taking.

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Appendix A**Table A.1. List of stimuli**

<i>Set 1</i>		
<i>Picture</i>	<i>Material</i>	<i>Valence</i>
Feather 1	Feather 1	Pleasant
Massage stone	Massage stone	Pleasant
Baby seal	Synthetic fur	Pleasant
Grass	Artificial grass	Pleasant
Pearls 1	Glass pearls 1	Pleasant
Lotus	Artificial blossom	Pleasant
Pebbles 1	Smooth pebbles	Pleasant
Soft toy (bear) 1	Teddy bear	Pleasant
Cotton	Cotton wool	Pleasant
Microfiber cloth	Soft towel	Pleasant
Dirty underwear	Cotton panties	Unpleasant
Dirty Socks 1	Wool socks	Unpleasant
Wet Hair	Synthetic hair	Unpleasant
Old condom 1	Soapy plastic	Unpleasant
Dead fish 1	Wet artificial fish 1	Unpleasant
Bone marrow 1	Prepared dog bone	Unpleasant
Used tissue 1	Prepared tissue 1	Unpleasant
Rotten apple 1	Prepared rubber foam 1	Unpleasant
Blob-fish	Wet artificial fish 2	Unpleasant
Earthworm	Artificial worm	Unpleasant
<i>Set 2</i>		
<i>Picture</i>	<i>Material</i>	<i>Valence</i>
Jellybeans	Jellybeans	Pleasant
Terrycloth 1	Soft cloth	Pleasant
Baby brush	Baby brush	Pleasant
Leaf	Artificial leaf	Pleasant
Soft toy (bear) 2	Teddy bear	Pleasant
Cat	Synthetic fur	Pleasant
Cotton plant	Cotton wool	Pleasant
Glass stones	Glass pearls 2	Pleasant
Massage tool	Wooden heart	Pleasant
Bunny	Cashmere shawl	Pleasant
Eel	Toy snake	Unpleasant
Rotten strawberry	Prepared rubber foam 2	Unpleasant
Bone marrow 2	Prepared dog bone	Unpleasant
Old condom 2	Soapy plastic	Unpleasant
Mushroom	Toy slime (red)	Unpleasant
Slug 1	Toy slime (green)	Unpleasant
Callused skin	Droughty citron	Unpleasant
Molded bread 1	Prepared dry bread	Unpleasant
Rotten apple 2	Prepared rubber foam 1	Unpleasant
Salamander	Toy lizard	Unpleasant
<i>Set 3</i>		
<i>Picture</i>	<i>Material</i>	<i>Valence</i>
Q-tip	Fresh Q-tip	Pleasant
Sheep	Wool	Pleasant
Cushion	Cushion	Pleasant
Hot-water bottle	Wrapped heating pad	Pleasant
Shaving brush	Make-up brush	Pleasant
Velvet 1	Velvet rag	Pleasant

SELF-OTHER DISTINCTION RTMS/FMRI

Angora	Angora wool ball	Pleasant
Wool ball 1	Wool ball 1	Pleasant
Pompom	Pompom	Pleasant
Terrycloth 2	Soft cloth	Pleasant
Dead fish 2	Wet artificial fish 1	Unpleasant
Used tissue 2	Prepared tissue 2	Unpleasant
Dead rat 1	Prepared synthetic fur 1	Unpleasant
Skin stretchmarks	Prepared artificial limb	Unpleasant
Maggots	Plastic maggots	Unpleasant
Used diaper	Prepared diaper	Unpleasant
Dirty socks 2	Wool socks	Unpleasant
Tongue	Toy slime (orange)	Unpleasant
Slug 2	Toy slime (green)	Unpleasant
Molded bread 2	Prepared dry bread	Unpleasant

Set 4

<i>Picture</i>	<i>Material</i>	<i>Valence</i>
Felt	Felt cloth	Pleasant
Wool ball 2	Wool ball 2	Pleasant
Pearls 2	Glass pearls 1	Pleasant
Pebbles 2	Smooth pebbles	Pleasant
Kitten	Synthetic fur	Pleasant
Rose	Artificial rose	Pleasant
Dog	Synthetic fur	Pleasant
Velvet 2	Velvet rag	Pleasant
Silk	Silk cloth	Pleasant
Feather 2	Feather 2	Pleasant
Mold	Harsh cotton wool	Unpleasant
Gullet	Prepared modelling clay	Unpleasant
Oyster	Shell with toy slime	Unpleasant
Dead rat 2	Prepared synthetic fur 2	Unpleasant
Centipede	Toy centipede	Unpleasant
Old chewing gum	Dry chewing gum	Unpleasant
Stinkbug	Plastic bug	Unpleasant
Old cigarette	Prepared cigarette filter	Unpleasant
Skin eruption	Prepared artificial limb 2	Unpleasant
Liver	Modelling clay	Unpleasant

Appendix B

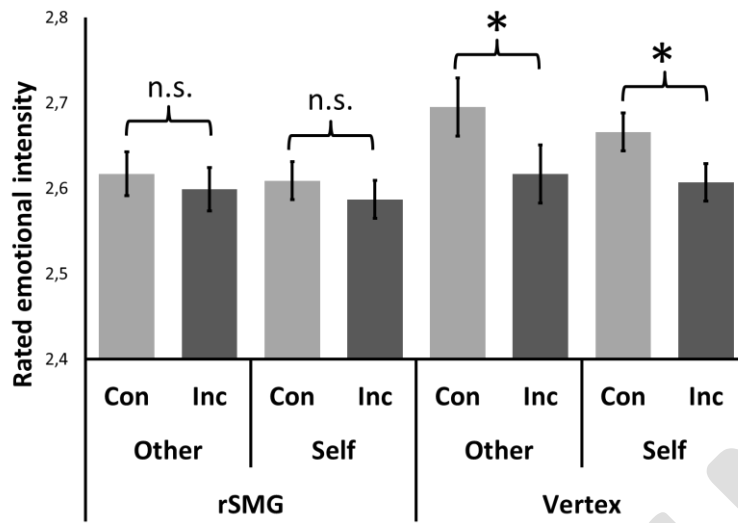


Figure B.1. Ratings in the rSMG and vertex (control) cTBS session (mean \pm 95% confidence intervals) show that participants were biased only in the vertex condition, irrespectively of whether participants judged the colleague's or the self-experienced emotion. A strong overall bias, or Congruency effect (i.e., lower emotional intensity in incongruent than congruent trials), indicates poor self-other distinction performance.

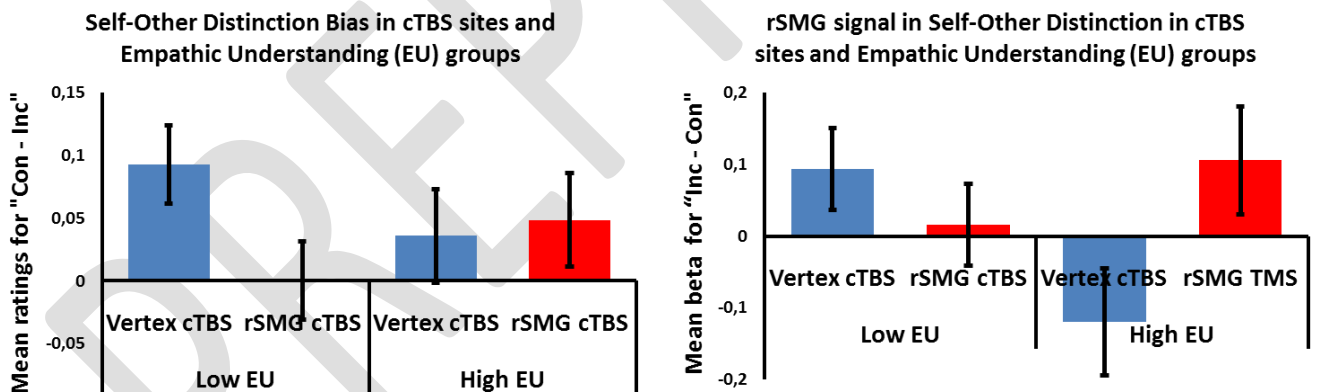


Figure B.2. Bar plots (means \pm 95% within IC) of self-other distinction performance (left panel) and rSMG BOLD signal (right panel) across cTBS sessions comparing high versus low dispositional empathic understanding participants (median split on 31 participants)

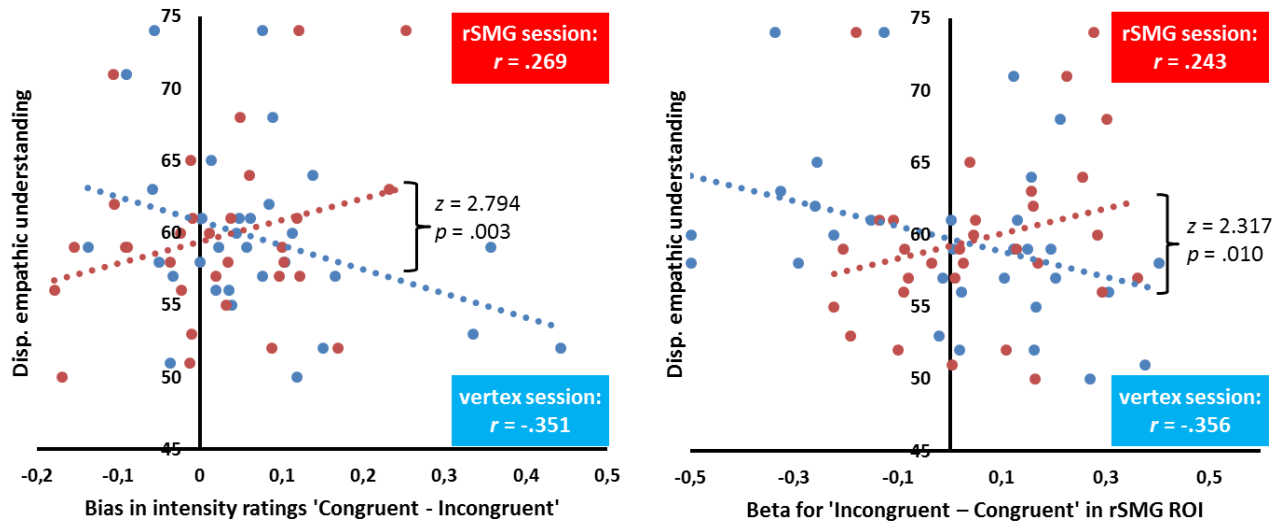


Figure B.3. Correlations between dispositional empathic understanding and self-other distinction performance (left panel) and rSMG BOLD signal (right panel) separately within the rSMG (red) and vertex (blue) cTBS sessions, and their statistical differences.